EXHIBIT 35

Arch Gynecol Obstet (2009) 280:925–931
DOI 10.1007/s00404-009-1030-3

ORIGINAL ARTICLE

Does long-term talc exposure have a carcinogenic effect on the female genital system of rats? An experimental pilot study

Nadi Keskın · Yasemin Aktan Teksen · Esra Gürlek Ongun · Yusuf Özay · Halil Saygılı

Received: 16 December 2008 / Accepted: 2 March 2009 / Published online: 20 March 2009

Abstract
Objective In several studies, the prolonged exposure to talc has been associated with development of ovarian cancer. However, some studies have advocated contrary views. The present study aims to investigate histopathological changes and whether long-term talc exposure is associated with potential carcinogenic effects on the female genital organs of rats.
Materials and methods The present study was conducted at Dumlupinar University Medical Faculty and a total of 28 Sprague–Dawley rats were included. The experimental animals were allocated into four groups having seven rats each. Groups 1 and 2 served as controls, where the rats in Group 1 did not receive any intervention and Group 2 received intravaginal saline. Groups 3 and 4 received intravaginal or perineal talc application, respectively. Talc was applied for 3 months on a daily basis. Histopathological changes in the peritoneum and female genital system were evaluated. For statistical analyses, Fisher's exact test was carried out using SPSS.
Findings In both the groups exposed to talc (Groups 3 and 4), evidence of foreign body reaction and infection, along with an increase in inflammatory cells, were found in all the genital tissues. Genital infection was observed in 12 rats in the study group and 2 rats in the control group. Neoplastic change was not found. However, there was an increase in the number of follicles in animals exposed to talc. No peritoneal change was observed. In the groups not exposed to talc, similar infectious findings were found, but there was a statistically significant difference between the groups (Groups 1 and 2 vs. Groups 3 and 4, $P > 0.05$). Neoplastic change was also not observed in these groups. Four groups were compared in terms of neoplastic effects and infections. In Groups 1, 5 rats were normal, two developed vulvovaginitis and endometritis with overinfection (in both ovaries), and one developed salpingitis (in both fallopian tubes), that is, infection was found in a total of two rats. In Group 2, only one experimental animal had endometritis. All the animals in Groups 3 and 4 developed infections.
Conclusions Talc has unfavorable effects on the female genital system. However, this effect is in the form of foreign body reaction and infection, rather than being neoplastic.

Keywords Talc · Ovary · Endometrium · Vulva

N. Keskın
Department of Obstetrics and Gynecology,
Dumlupınar University Medical Faculty, Kütahya, Turkey

Y. A. Teksen
Department of Pharmacology,
Dumlupınar University Medical Faculty, Kütahya, Turkey

E. G. Ongun
Department of Pathology,
Dumlupınar University Medical Faculty, Kütahya, Turkey

Y. Özay
College of Health Science, Ahi Evran University, Kirsehir, Turkey

H. Saygılı
Department of Obstetrics and Gynecology,
İstanbul Medical Faculty, İstanbul University, Istanbul, Turkey

N. Keskın (✉)
Dumlupınar Üniversitesi Tıp Fakültesi Hastanesi
Kadın Hastalıkları ve Doğum Anabilim Dalı Kütahya,
Tavşanlı yolu 10. km merkez kampusu, Kuhtiya, Turkey
e-mail: nadikeskin@superonline.com

Introduction

Various factors have been cited in the development of genital cancers. Many studies have been conducted regarding the potential role of talc in ovarian cancer and previously it had been widely accepted as an important etiological factor [1–4]. In recent years, some studies (meta-analysis) have been averse toward this concept [5, 6]. Asbestos is a well-known carcinogen, and described as having a particular role in the development of pleural and peritoneal mesothelioma [7]. Its association with ovarian cancer has also been demonstrated in several studies [8–10].

Talc and asbestos are both silicate minerals. Minerals are classified according to their anionic structure, and its subclasses are defined by chemical composition or structure. Classes and subclasses can be further divided into mineral groups on the basis of atomic structure and chemical similarities. Talc is a magnesium silicate hydroxide, characterized by water molecules trapped between silicate sheets, which belongs to the silicate subclass phyllosilicate and the clay group montmorillonite/smectite. The three other major phyllosilicate clay groups are kaolinite/serpentine, illite, and chlorite [5].

Asbestos is the generic or commercial name for six naturally occurring fibrous minerals including amosite, chrysotile, and crocidolite, which are used in industrial applications, and the fibrous varieties of tremolite, actinolite, and anthophyllite. Asbestos is morphologically distinct from talc and belongs to different silicate mineral groups and subgroups. The carcinogenic effects of asbestos have been extensively studied and documented in medical literature [10, 11]. It is clear that the morphologic structure of serpentine asbestos and the fibrous form of amphiboles is responsible for their carcinogenic properties, much more than its atomic constituents [12]. In contrast, talc, which is a member of the montmorillonite/smectite group, rarely occurs in the asbestiform habit (a mineral's fibrous pattern of growth). Even asbestiform talc is not as carcinogenic as asbestos owing to its chemical and physical properties [5].

Although a number of studies have examined the relation between talc and ovarian cancer, its effect on other female genital system tissues have not been investigated. In addition, the carcinogenic effect of talc has not been ascertained. The present experimental study aimed to examine carcinogenic effects of long-term talc exposure on genital system of female Sprague–Dawley rats.

Materials and methods

Experimental animals

The experimental study was conducted at Dumlupınar University Medical Faculty and approved by the institutional ethics committee for animal experiments. A total of 28 Sprague–Dawley female rats weighing 200–250 g were used as experimental animals. Animals were kept in standard cages at room temperature under normal diurnal conditions (12 h day and 12 h night). Sufficient water and food intake was provided.

Groups

The experimental animals were assigned into four different groups having seven rats each. Group 1 served as control and did not receive any intervention. Group 2 also served as control and 0.5 ml of saline was intravaginally administered to these animals. Groups 3 and 4 were study groups and received intravaginal and perineal talc application (100 mg in 0.5 ml of saline), respectively. Talc with saline was given in aerosol form to the animals; dust form was not applied. However, this application can be optimally intravaginal. Talc application was done daily for 3 months. At the beginning of the study, cervicovaginal smear samples were obtained from each animal between 08:00 and 09:00 a.m.

Histopathological examination

At the end of the experiment, the animals were sacrificed under ether anesthesia by drawing blood from their hearts thus inducing hypovolemic shock. All the internal and external genital organs (vulva, vagina, uterus, fallopian tubes, and ovaries) were surgically removed and placed in 10% formaldehyde solution. The samples were examined for the changes in the peritoneum and female genital system. Hematoxylin and eosin (H&E) staining and light microscopy was used in the histopathological examination. For statistical analysis, Fisher's exact test was performed using the SPSS software. A P value <0.05 was considered significant.

Findings

Baseline smears revealed the presence of vaginitis in only two experimental animals, whereas findings were normal for the remaining 26 rats. One of the rats detected with vaginitis belonged to the study group and one of them belonged to the control group. At baseline, the mean weight of all rats was 226 ± 24 g (average weight of study groups was 228 ± 18 g, control groups was 224 ± 30 g) and the corresponding figure at the end of 3 months was 240 ± 20 g (229 ± 17 g study groups, 251 ± 23 g were found in the control groups) showing no significant change.

Foreign body reaction, findings of infection, and increased number of inflammatory cells were found in all groups exposed to talc (Groups 3 and 4). No neoplastic

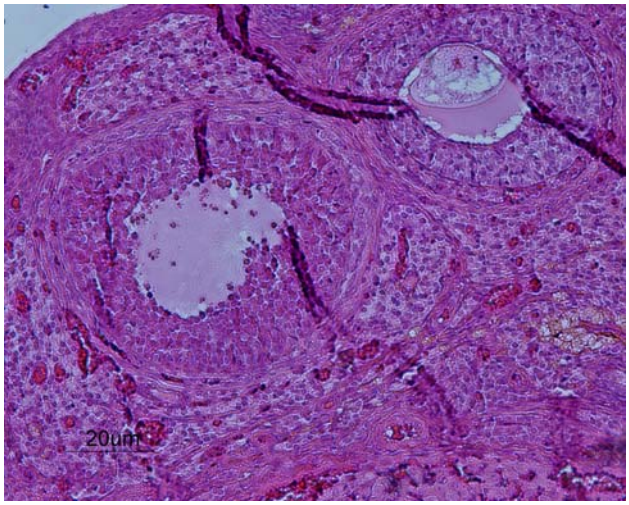

Fig. 1 An increase in the number of follicles was observed in the ovaries

change or peritoneal change was detected. Moreover, an increase in the number of follicles was observed in the ovaries of all animals in the control and study groups. (Fig. 1)

The four groups were compared in terms of neoplastic effects and infections. In Groups 1, 5 rats were normal, two developed vulvovaginitis and endometritis with over infection (in both ovaries), and one developed salpingitis (in both fallopian tubes). Infection was found in two rats. In Group 2, only one experimental animal had endometritis. In Groups 3 and 4, all the animals developed infection. Animals in Group 3 developed the following pathologies: vulvovaginitis ($n = 5$), endometritis ($n = 6$), pelvic infection ($n = 4$), ovarian infection (a total of 7 ovaries in 3 animals), and salpingitis and tubal occlusion ($n = 8$). In Group 4, all seven rats developed vulvovaginitis; furthermore, four developed endometritis, five developed pelvic infection, four developed ovarian infection (in eight ovaries), and two developed salpingitis and tubal occlusion (one unilateral and one bilateral). The analysis using Fisher's exact test showed positive correlations between following groups: Group 3 and Group 1, Group 3 and Group 2, Group 4 and Group 1, and Group 4 and Group 2 ($P < 0.05$). Other pairwise comparisons did not reveal significant results ($P > 0.05$) (Table 1).

Conclusions

The preliminary results show that in 28 rats from the 4 groups, talc had unfavorable effects on the female genital system. However, this effect seems to be in the form of foreign body reaction or infection rather than a neoplastic change. The results of previous studies are in favor of a neoplastic effect, particularly on the ovaries. However, more experimental and clinical studies are warranted to reach firm conclusions. In the study and control groups used in this research, an increase in follicle number was also observed. It should be emphasized that other environmental factors may have role in these effects. Therefore, the effect of different study conditions should also be investigated in detail.

Declaration

The present study was designed and conducted by Nadi Keskin MD, with the contributions and approval of Prof. Halil Saygili MD, an academic member of the Istanbul Medical Faculty, Istanbul University, as an extended study of 'Histopathological Changes Induced by talc Exposure in Rats' [9] previously published in 'Endokrinolojide Yönelisler Dergisi' (2005; volume 14, number 4). The language of this manuscript was edited by SPi Professional Editing Services (http://www.prof-editing.com/index.php).

Table 1 Groups of histopathological changes observed in the genital system of experimental animals

	Normal	Vulvovaginitis	Endometritis	P ID	Findings of ovarian infection ($n = 2 \times 7 = 14$)	Salpingitis and tubal occlusion ($n = 2 \times 7 = 14$)	Neoplastic changes	Preneoplastic changes
Group 1 ($n = 7$)	5	2	0	1	1 (2 ovaries)	1 (2 fallopian tubes)	0	0
Group 2 ($n = 7$)	6	0	1	0	0	0	0	0
Group 3 ($n = 7$)	0	5	6	4	7 ($2 \times 3 + 1$)*	8 (2×4)	0	0
Group 4 ($n = 7$)	0	7	4	5	8 (2×4)	5 ($2 \times 2 + 1$)**	0	0

Statistical comparisons of the groups were done by using Fischer exact test. Following positive correlations were found between groups: Group 3 and Group 1, $P = 0.021$, $P < 0.05$; Group 3 and Group 2, $P = 0.005$, $P < 0.05$; Group 4 and Group 1, $P = 0.021$, $P < 0.05$, Group 4 and Group 2, $P = 0.005$, $P < 0.05$. Other comparisons did not reveal statistically significant results ($P > 0.05$)

Group 1: control group with no intervention, Group 2: control group receiving intravaginal saline administration, Group 3: study group receiving intravaginal talc application, Group 4: study group receiving perineal talc application

* In this group, one rat had infection findings in only one ovary. For the remaining, both ovaries were involved, ** In this group, one rat had infection findings in only one fallopian tube

Discussion

Various etiological factors have been cited for genital cancers. A number of studies on talc have been conducted to investigate its effect on the development of ovarian cancer, the most fatal among these malignancies; it is commonly accepted as an important etiological factor for this cancer [1–4]. In recent years, some studies (meta-analysis) have been averse to defend this concept [5, 6]. Asbestos is a well-known carcinogen that has a particular role in the development of pleural or peritoneal mesothelioma. It has also been associated with ovarian cancer [8–10]. However, because of differences in the structure of talc and asbestos, the carcinogenic effect of asbestos has also been examined.

Talc is an important industrial material, because of its resistance to electricity, heat, and acid. Therefore, it is widely used in plastic surfaces, especially in surgical gloves, various plastic apparatus, and gynecologic services, and women are commonly known to use it for sanitation purposes. Other applications for talc include contraceptive diaphragms and condoms [5], and the treatment of pleural effusions and pleurodynia [13–15].

Surveys on the hygienic practices of women and talc application on the perineum, animal experiments, and clinical trials are among the studies that investigate the carcinogenic effects of talc [16, 17]. Since the first study showing an almost twofold increase in the risk of ovarian cancer with any perineal talc use [3], most case-control studies have demonstrated positive associations with talc use [4, 18]. Not all of them have been statistically significant [19–21]. Several studies [21–23] did not find an overall association between any genital talc use and ovarian cancer. Some studies [21, 22, 24] have demonstrated statistically insignificant trends in risk with increased frequency of talc use, duration of use, and measures of "total lifetime applications," whereas other studies [19, 20] have not observed a statistically significant dose response. With regard to histologic subtypes, a recent study by Cramer et al. [24] observed the greatest risk of talc use in invasive serous cancer; however, other studies have found increased risks for endometrioid cancers [4, 21], serous cancers [25], and invasive cancers of all subtypes [4]. Because serous cancers which account for over half of all invasive ovarian cancers, most resemble mesotheliomas, it could be hypothesized that this subtype may be most likely associated with talc use.

There have been few studies [26, 27] of talc exposure in animals and these studies have not demonstrated an increase in ovarian cancer among animals subjected to continuous talc exposure. These data should be interpreted cautiously because there are important anatomic and physiologic differences between rodents and humans. In animals, talc is often administered at high dose via aerosol exposure [26].

Some studies found a positive relation between ovarian cancer and perineal talc application. Cramer et al. [3], Rosenblatt et al. [28], and Chang et al. [4] have reported relative risks of 1.92 (%95 CI 1.3–2.9), 2.4 (%95 CI 1.1–5.3), and 1.42 (%95 CI 1.08–1.86), respectively. This shows an increased risk correlation between the use of talc as a cosmetic and ovarian cancer, but this increased risk is not significant. Studies by Cramer et al. describe the relationship between talc and ovarian cancer; thus, "Our studies have suggested an increased risk for ovarian cancer associated with the use of talcum powder in genital hygiene, but the biologic credibility of the association has been questioned."

In a meta-analysis, Huncharek implied that earlier epidemiological studies suggest an association between perineal cosmetic talc use and increased risk of epithelial ovarian cancer. This meta-analysis was performed to evaluate such an association. Available observational data do not support the existence of a causal relationship between perineal talc exposure and an increased risk of epithelial ovarian cancer [5]. Selection bias and uncontrolled confounding may account for positive associations observed in prior epidemiological studies. In addition, in a review, Muscat implied that talc is not genotoxic. Mechanistic, pathology, and animal model studies have not found evidence of a carcinogenic effect. In summary, these data collectively do not indicate that cosmetic talc causes ovarian cancer [6].

Talc has been used routinely in humans in the treatment of pleural effusions, where talc is directly applied to the human pleura. Long-term follow-up studies of humans undergoing this procedure have not shown a single case of malignancy induced by talc [13–15].

Animal data in relation to talc toxicity are important: Wagner et al. [29] used Italian talc in experimental animal study; Italian talc has been tested on rats using three routes, intra-pleural inoculation, inhalation, and ingestion. Groups exposed to superfine chrysotile asbestos and untreated controls were included for comparison. In all the experiments, animals were allowed to live out their lives. The intra-pleural inoculation of talc produced no mesotheliomas in contrast to 18 produced by the chrysotile asbestos. After ingestion, one leiomyosarcoma occurred with Italian talc and one with chrysotile asbestos. Whether these tumors are a consequence of the feeding is uncertain. The inhalation studies demonstrated that with equal dosage, talc can produce a similar amount of fibrosis as asbestos. However, the chrysotile-exposed rats developed lung adenomas, adenomatosis, and an adenocarcinoma, whereas the only lung tumor seen in animals exposed to talc was a small adenoma, which may have been an incidental finding. In another experimental animal study [30], 256 Wistar rats received a single injection of crocidolite into the right pleural cavity to induce mesotheliomas. Subsequently, they

were given right intra-pleural injections of BCG, crystalline silica, talc, carrageenan, or saline (as a control). There was no significant change in the mesothelioma rate in the rats exposed to BCG, silica or talc, but there was a threefold increase in mesothelioma incidence in the group injected with carrageenan.

Wagner, Huncharek, Hill, Muscat, and others hold that talc is not carcinogenic. Also in this study, carcinogenic effect of talc has not been determined either in any female rat genital system tissue or in ovary tissue.

In an experimental study on rats, Henderson et al. [31] demonstrated the presence of talc in the ovaries following vaginal talc application. Similarly, in the study of Egli et al. [32], carbon particles reached the fallopian tubes in 30–35 min. Therefore, talc disseminates to vulvovaginal region, endometrium, fallopian tubes, ovaries, and peritoneum after vaginal examination, raising the possibility of changes—even preneoplastic or neoplastic—due to talc exposure following perineal or vaginal talc application. Langseth et al. [33] are skeptical about the association between perineal talc application and ovarian cancer. In their article, Langseth et al. expressed that the origin of ovarian cancer is multifactorial, especially breast cancer patients who are BRCA 1 and BRCA 2 gene carriers, who have increased the risk of ovarian cancer. Therefore, the role of environmental factors such as talc and asbestos in cancer formation is suspected of being over stressed.

Salazar et al. examined histological changes in BRCA 1 gene positive women who underwent prophylactic oophorectomy because of their high inherited risk of ovarian cancer, and reported the following findings: increased follicular activity, hyperplasia of corpus luteum, hilar cell hyperplasia, pseudostratification of superficial epithelium, superficial papillomatosis, cortical stromal hyperplasia, and hyperkeratosis. These investigators defined increased follicular activity, hyperplasia of corpus luteum, and other findings as preneoplastic phenotypes in ovaries with high risk [34]. If talc application has a carcinogenic effect on ovaries, this study would also obtain similar findings. In the present study, experimental animals exposed to talc both via vaginal and perineal application for 3 months did not show the abovementioned changes except for an increased number of follicles. Although both the control and study groups showed an increase in follicle number, thus it was not attributed to talc application; however, the increase in follicle number could not be explained as well. Therefore, this study did not demonstrate an association between talc application and peritoneal/ovarian cancer.

In both groups exposed to talc (Groups 3 and 4), evidence of foreign body reaction and infection along with an increase in inflammatory cells were found in all the genital tissues. Muscat comments on this [6]: “Given the dissimilarities between talc and asbestos with regard to their fibrous shapes, the weak but increased associations in the epidemiologic studies could be attributed to other mechanisms assuming that the statistical associations are unbiased and not due to confounding. Asbestos fibers in the lung initiate an inflammatory and scarring process, and it has been proposed that ground talc, as a foreign body, might initiate an inflammatory response [35]. Pelvic inflammatory diseases, however, such as endometritis, peritonitis, tubo-ovarian access formation, and salpingo-oophoritis have in general not been associated with an increased risk of ovarian cancer.”

Similar to Muscat’s comments, this study also demonstrated unfavorable effects of talc on female genital system; however, it was in the form of foreign body reaction, infection, or increased adhesions, rather than neoplastic. In addition, the authors of this study believe that talc may have caused foreign body reaction, infection, or increased adhesions, which should be important for infertile patients.

Endometrial cancer is the most common genital malignancy among women. Unbalanced estrogen levels are being blamed for its etiology [36]. Various physical and chemical factors have also the potential to initiate preneoplastic and neoplastic stimulus [37]. A literature search did not reveal any study examining such an effect of talc on the endometrium. However, this study could not demonstrate any preneoplastic or neoplastic effect of talc on endometrial tissue.

Etiological factors for vulvar, vaginal, and cervical cancers have been largely discovered; in particular, HPV (Human Papilloma Virus) has been identified as an etiological factor [38]. In addition, physical and chemical factors have also been held responsible. However, talc is not counted among these factors and a clinical study examining such an effect does not exist. None of the rats in this study showed an evidence of such an effect.

Talc application has unfavorable effects on female genital system, particularly on ovaries and fallopian tubes. This usually manifests itself in the form of tissue injury, macrophage infiltration, and an increased rate of infections and development of adhesions [8, 39–41]. Holmdahl [42] emphasized the important role of talc in the development of adhesions after intraperitoneal surgery. Merritt et al. [8] reported an increase in chronic pelvic infections following perineal talc application. Ellis et al. [43] also emphasized the unfavorable effects of talc spilling from surgical gloves. In the present study, compared to the controls, a significantly increased rate of infection was found among the rats exposed to talc, which was particularly prominent for endometrial tissue, uterine tubes, and pelvic peritoneum. These tissues exhibited epithelial tissue injury, macrophage infiltration, and adhesions. Tubal adhesions are important in the context of infertility. In addition, the high rate of vulvovaginitis may have important implications for patients undergoing frequent gynecological examinations and for

immunocompromised patients attending outpatient gynecological oncology clinics.

In conclusion, the present study demonstrated unfavorable effects of talc on female genital system in the form of foreign body reaction, infection, or increased adhesions, rather than neoplastic. Moreover, the authors believe that talc may have a stimulating effect on ovaries, which should be further investigated particularly in infertile patients. However, the authors of this study highlight the fact that other environmental factors may have role in the increased follicle number presented by the control group. Therefore, separate intensive studies in the series, to demonstrate the effect of talc on the ovary should be considered.

Conflict of interest statement None.

References

1. Longo DL, Young RC (1979) Cosmetic talc and ovarian cancer. Lancet 2:1011–1012. doi:10.1016/S0140-6736(79)92576-5
2. Graham J, Graham R (1967) Ovarian cancer and asbestos. Environ Res 1:115–128. doi:10.1016/0013-9351(67)90008-4
3. Cramer DW, Welch WR, Scully Re, Wojciechoski CA (1982) Ovarian cancer and talc: a case control study. Cancer 50:37–60. doi:10.1002/1097-0142(19820715)50:2<372::AID-CNCR2820500235>3.0.CO;2-S
4. Chang S, Risch HA (1997) Perineal talc exposure and risk of ovarian carcinoma. Cancer 79:2396–2401. doi:10.1002/(SICI)1097-0142(19970615)79:12<2396::AID-CNCR15>3.0.CO;2-M
5. Huncharek MS, Muscat J, Ontilio A, Kupelnick B (2007) Use of cosmetic talc on contraceptive diaphragms and risk of ovarian cancer: a meta-analysis of nine observational studies. Eur J Cancer Prev 16(5):422–429. doi:10.1097/01.cej.0000236257.03394.4a
6. Muscat JE, Huncharek MS (2008) Perineal talc use and ovarian cancer: a critical review. Eur J Cancer Prev 17(2):139–146
7. Dunnigan J (1988) Linking chrysotile asbestos with mesothelioma. Am J Ind Med 14(2):205–209. doi:10.1002/ajim.4700140211
8. Merritt MA, Green AC, Nagle CM, Webb PM, Study Australian Cancer (2008) Ovarian Cancer: Australian Ovarian Cancer Study Group Talcum powder, chronic pelvic inflammation and NSAIDs in relation to risk of epithelial ovarian cancerInt. J Cancer 122(1):170–176
9. Saygılı H, Citil I, Bilir A (2005) Farelerde talk maruziyetinin overde neden olduğu histopatolojik değişiklikler. Endorinolojide Yönelişler Dergisi 14:4
10. Huncharek M (1986) The biomedical and epidemiological characteristics of asbestos-related diseases: a review. Yale J Biol Med 59(4):435–451
11. Mossman BT, Gee JB (1989) Asbestos-related diseases. N Engl J Med 320(26):1721–1730
12. Stanton MF, Layard M, Tegeris A et al (1981) Relation of particle dimension to carcinogenicity in amphibole asbestoses and other fibrous minerals. J Natl Cancer Inst 67(5):965–975
13. Genofre EH, Marchi E, Vargas FS (2007) Inflammation and clinical repercussions of pleurodesis induced by intrapleural talc administration. Clinics 62(5):627–634. doi:10.1590/S1807-59322007000500015
14. Kolschmann S, Ballin A, Juergens UR, Rohde G, Gessner C, Hammerschmidt S, Wirtz H, Gillissen A (2006) Talc pleurodesis in malignant pleural effusions. Pneumologie 60(2):89–95. doi:10.1055/s-2005-919139
15. Marchi E, Vargas FS, Acencio MM, Antonangelo L, Teixeira LR, Genofre EH, Light RW (2004) Talc and silver nitrate induce systemic inflammatory effects during the acute phase of experimental pleurodesis in rabbits. Chest 125(6):2268–2277. doi:10.1378/chest.125.6.2268
16. Tzonou A, Polychronopoulou A, Hsieh CC, Rebelakos A, Karakatsani A, Trichopoulos D (1993) Hair dyes, analgesics, tranquilizers and perineal talc application as risk factors for ovarian cancer. Int J Cancer 55:408–410. doi:10.1002/ijc.2910550313
17. Mills PK, Riordan DG, Cress RD, Young HA (2004) Perineal talc exposure and epithelial ovarian cancer risk in the Central Valley of California. Int J Cancer 112(3):458–464. doi:10.1002/ijc.20434
18. Chen Y, Wu PC, Lang JH, Ge WY, Hartge P, Brinton LA (1992) Risk factors for epithelial ovarian cancer in Beijing, China. Int J Epidemiol 21:23–29. doi:10.1093/ije/21.1.23
19. Whittemore AS, Wu ML, Paffenbarger RS Jr et al (1988) Personal and environmental characteristics related to epithelial ovarian cancer. II. Exposures to talcum powder, tobacco, alcohol, and coffee. Am J Epidemiol 128:1228–1240
20. Booth M, Beral V, Smith P (1989) Risk factors for ovarian cancer: a case-control study. Br J Cancer 60:592–598
21. Harlow BL, Cramer DW, Bell DA, Welch WR (1992) Perineal exposure to talc and ovarian cancer risk. Obstet Gynecol 80:19–26
22. Hartge P, Hoover R, Lesher LP, McGowan L (1983) Talc and ovarian cancer. JAMA 250:1844 (letter). doi:10.1001/jama.250.14.1844
23. Wong C, Hempling RE, Piver MS, Natarajan N, Mettlin CJ (1999) Perineal talc exposure and subsequent epithelial ovarian cancer: a case-control study. Obstet Gynecol 93:372–376. doi:10.1016/S0029-7844(98)00439-6
24. Cramer DW, Liberman RE, Titus-Ernstoff L et al (1999) Genital talc exposure and risk of ovarian cancer. Int J Cancer 81:351–356. doi:10.1002/(SICI)1097-0215(19990505)81:3<351::AID-IJC7>3.0.CO;2-M
25. Cook LS, Kamb ML, Weiss NS (1997) Perineal powder exposure and the risk of ovarian cancer. Am J Epidemiol 145:459–465
26. Boorman GA, Seely JC (1995) The lack of an ovarian effect of lifetime talc exposure in F344/N rats and B6C3F1 mice. Regul Toxicol Pharmacol 21:242–243. doi:10.1006/rtph.1995.1035
27. Hamilton TC, Fox H, Buckley CH, Henderson WJ, Griffiths K (1984) Effects of talc on the rat ovary. Br J Exp Pathol 65:101–106
28. Rosenblatt KA, Szklo M, Rosenshein NB (1992) Mineral fiber exposure and the development of ovarian cancer. Gynecol Oncol 45:20–25. doi:10.1016/0090-8258(92)90485-2
29. Wagner JC, Hill RJ, Berry G, Wagner MM (1980) Treatments affecting the rate of asbestos-induced mesotheliomas. Br J Cancer 41(6):918–922
30. Wagner JC, Berry G, Cooke TJ, Hill RJ, Pooley FD, Skidmore JW (1980) Animal experiments with talc. Br J Cancer 41(6):918–922
31. Henderson WJ, Hamilton RC, Griffiths K (1979) Talc in normal and malignant ovarian tissue. Lancet 1:499. doi:10.1016/S0140-6736(79)90860-2
32. Egli GE, Newton M (1961) The transport of carbon particles in the human female reproductive tract. Fertil Steril 12:151–155
33. Langseth H, Hankinson SE, Siemiatycki J, Weiderpass E (2008) Perineal use of talc and risk of ovarian cancer. J Epidemiol Community Health 62(4):358–360. doi:10.1136/jech.2006.047894
34. Salazar H, Godwin AK, Daly MB, Laub PB (1996) Microscopic benign and invasive malignant neoplasm and a cancer-prone phenotype in prophylactic oophorectomies. J Natl Cancer Inst 88(24):1810–1820. doi:10.1093/jnci/88.24.1810
35. Ness RB, Cottreau C (1999) Possible role of ovarian epithelial inflammation in ovarian cancer. J Natl Cancer Inst 91(17):1459–1467. doi:10.1093/jnci/91.17.1459
36. Balmer NN, Richer JK, Spoelstra NS, Torkko KC, Lyle PL, Singh M (2006) Steroid receptor coactivator AIB1 in endometrial

carcinoma, hyperplasia and normal endometrium: correlation with clinicopathologic parameters and biomarkers. Mod Pathol 19(12):1593–1605. doi:10.1038/modpathol.3800696
37. Schumacher (1956) Talc granuloma of the endometrium. Geburtshilfe Frauenheilkd 16(12):1082–1098
38. Riethmuller D, Guerrini JS, Aubin F (2007) Intraepithelial lesions and neoplasia associated with human papillomavirus infection. Bull Acad Natl Med 191(3):601–609 (discussion pp 609)
39. Scully RE, Young RH, Clement PB (1998) Tumors of the ovary, maldeveloped gonads, fallopian tube and broad ligament. In: Atlas of tumor pathology, fascicle 23, 3rd series. Armed Forces Institute of Pathology, Washington
40. Kyzer S, Gelber E, Koren R, Chaimoff C (1994) Peritoneal band containing talc: rare cause of small bowel obstruction in a previously unoperated child. J Pediatr Surg 29(12):1616–1617. doi:10.1016/0022-3468(94)90239-9
41. Regodón Vizcaino J, Fernández Yuste J, Rodríguez Sánchez E, Carbajo Vicente M (1982) Peritoneal lesions caused by powder from surgical gloves (talc and starch. Rev Esp Enferm Apar Dig 62(5):424–430
42. Holmdahl L, Risberg B, Beck DE, Burns JW, Chegini N, di Zerega GS, Ellis H (1997) Adhesions: Pathogenesis and prevention-panel discussion and summary. Eur J Surg Suppl (577):56–62
43. Ellis H (1990) The hazards of surgical glove dusting powders. Surg Gynecol Obstet 171(6):521–527